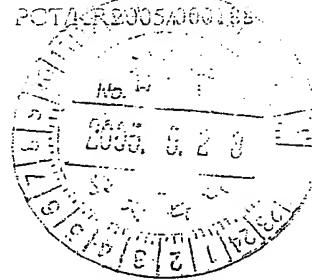


## PATENT COOPERATION TREATY

PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)



Applicant's or agent's file reference 5fpo-01-08	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. <b>PCT/KR2005/000188</b>	International filing date (day/month/year) <b>20 JANUARY 2005 (20.01.2005)</b>	(Earliest) Priority Date (day/month/year) <b>20 JANUARY 2004 (20.01.2004)</b>
Applicant <b>KOREA RESEARCH INSTITUTE OF BIOSCIENCE AND BIOTECHNOLOGY et al</b>		

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report
  - a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 

The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
  - b.  With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.
2.  Certain claims were found unsearchable (See Box No. II)
3.  Unity of invention is lacking (See Box No. III)
4. With regard to the title,
 

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the drawings,
  - a. the figure of the drawings to be published with the abstract is Figure No. 4

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.
  - b.  none of the figure is to be published with the abstract.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR2005/000188

## Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of :

## a. type of material

a sequence listing  
 table(s) related to the sequence listing

## b. format of material

in written format  
 in computer readable form

## c. time of filing/furnishing

contained in the international application as filed  
 filed together with the international application in computer readable form  
 furnished subsequently to this Authority for the purposes of search

2.  In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

## 3. Additional comments:

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/KR2005/000188

## A. CLASSIFICATION OF SUBJECT MATTER

## IPC7 C12N 15/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7 C12N 15/12, A61K 38/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean Patents and applications for inventions since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NCBI PubMed, Esp@cenet, CA "differentiation regulating agent, stem cell, natural killer cell"

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GUO W. et al., 'A human Mix-like homeobox gene MDX1 shows functional similarity to Xenopus Mix.1', In: Blood, 2002, Vol. 100(1), pp. 89-95. see the whole document	1-7
A	DAVIDSON A.J. & ZON L.I., 'Turning mesoderm into blood: the formation of hematopoietic stem cells during embryogenesis', In: Curr. Top. Dev. Biol., 2000, Vol. 50, pp. 45-60 see the whole document	1-7
A	OGAWA M. et al., 'Expression of a 4-integrin defines the earliest precursor of hematopoietic cell lineage diverged from endothelial cells', In: Blood, 1999, Vol. 93(4), pp. 1168-1177 see the whole document	1-7
A	ALLEN R.D. et al., 'c-Myb is essential for early T cell development', In: Genes & Dev., 1999, Vol. 13(9), pp. 1073-1078 see the whole document	1-7
A	KLEFSTROM J. et al., 'c-Myc and E1A induced cellular sensitivity to activated NK cells involves cytotoxic granules as death effectors', In: Oncogene, 1999, Vol. 18(13), pp. 2181-2188 see the whole document	1-7

 Further documents are listed in the continuation of Box C. See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"E" document member of the same patent family

Date of the actual completion of the international search

20 MAY 2005 (20.05.2005)

Date of mailing of the international search report

20 MAY 2005 (20.05.2005)

Name and mailing address of the ISA/KR


 Korean Intellectual Property Office  
920 Dunsan-dong, Seo-gu, Daejeon 302-701,  
Republic of Korea

Facsimile No. 82-42-472-7140

Authorized officer

CHO, YOUNG GYUN

Telephone No. 82-42-481-8132



## PATENT COOPERATION TREATY

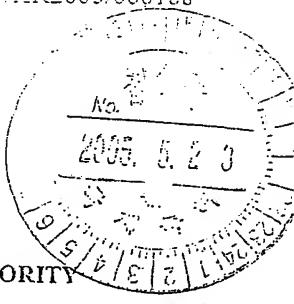
From the  
INTERNATIONAL SEARCHING AUTHORITY

To: LEE, Won-Hee
8th Fl. Sung-ji Heights II 642-16 Yoksam-dong Kangnam-ku Seoul 135-080 Republic of Korea

PCT

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)



Date of mailing  
(day/month/year) 20 MAY 2005 (20.05.2005)

Applicant's or agent's file reference 5fpo-01-08	FOR FURTHER ACTION See paragraph 2 below	
International application No. <b>PCT/KR2005/000188</b>	International filing date (day/month/year) <b>20 JANUARY 2005 (20.01.2005)</b>	Priority date(day/month/year) <b>20 JANUARY 2004 (20.01.2004)</b>
International Patent Classification (IPC) or both national classification and IPC <b>IPC7 C12N 15/12</b>		
Applicant <b>KOREA RESEARCH INSTITUTE OF BIOSCIENCE AND BIOTECHNOLOGY et al</b>		

## 1. This opinion contains indications relating to the following items:

<input checked="" type="checkbox"/> Box No. I	Basis of the opinion
<input type="checkbox"/> Box No. II	Priority
<input type="checkbox"/> Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
<input type="checkbox"/> Box No. IV	Lack of unity of invention
<input checked="" type="checkbox"/> Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
<input type="checkbox"/> Box No. VI	Certain documents cited
<input type="checkbox"/> Box No. VII	Certain defects in the international application
<input type="checkbox"/> Box No. VIII	Certain observations on the international application

## 2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later. For further options, see Form PCT/ISA/220.

## 3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/KR

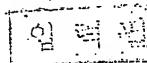
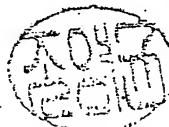
 Korean Intellectual Property Office  
920 Dunsan-dong, Seo-gu, Daejeon 302-701,  
Republic of Korea

Facsimile No. 82-42-472-7140

Authorized officer

CHO, YOUNG GYUN

Telephone No. 82-42-481-8132



WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/KR2005/000188

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

a sequence listing  
 table(s) related to the sequence listing

b. format of material

in written format  
 in computer readable form

c. time of filing/furnishing

contained in the international application as filed.  
 filed together with the international application in computer readable form.  
 furnished subsequently to this Authority for the purposes of search.

3.  In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/KR2005/000188

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-7	YES
	Claims	None	NO
Inventive step (IS)	Claims	1-7	YES
	Claims	None	NO
Industrial applicability (IA)	Claims	1-7	YES
	Claims	None	NO

2. Citations and explanations :

The following documents have been considered for the purpose of this written opinion:

D1: Blood, Vol. 100(1), pp. 89-95 (2002)  
 D2: Curr. Top. Dev. Biol., Vol. 50, pp. 45-60 (2000)  
 D3: Blood, Vol. 93(4), pp. 1168-1177 (1999)  
 D4: Genes & Dev., Vol. 13(9), pp. 1073-1078 (1999)  
 D5: Oncogene, Vol. 18(13), pp. 2181-2188 (1999)

D1 discloses a human Mix-like homeobox gene expression restricted to immature B and T cells. D1 generally mentions that the gene may be involved in hematopoietic fate through the SCL regulation, which is one of the factor required for the differentiation of uncommitted hematopoietic progenitors with high precision. The assumption is based on the fact that the Xenopus Mix.1 induces expression of Xenopus SCL.

D2 also discloses the involvement of the members of the Mix of homeobox transcription factor in the induction of ventral mesoderm, where the formation of hematopoietic stem cells during development occurs.

D3 discloses the Gata2 and Myb genes correlated with the potential of the  $\alpha$ 4-integrin cells to give rise to hematopoietic cell differentiation, which is the molecule expressed on a hematopoietic stem cell.

D4 reveals the importance of the c-Myb transcription factor for fetal hematopoiesis and early stages of T-cell development by studying transgenic null mice.

D5 discloses that the oncoproteins c-Myc and E1A render cells vulnerable to NK cell mediated cytosis, which means the activation of the function of NK cells.

(Continued on Supplemental Sheet.)

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/KR2005/000188

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Box No. V

I. Novelty

The present invention relate to a composition containing a gene regulating differentiation from stem cells into natural killer cells as an effective ingredient. Even though the prior art documents disclose the suggestive result which is related to the involvement of those genes in hematopoietic lineage, none of the prior art documents disclose that they directly regulate differentiation from stem cells into natural killer cells.

Therefore, the subject matter of claims 1-7 is considered to be novel under PCT Article 33(2).

II. Inventive Step

D1 and D2 suggest the Mix-like homeobox gene regulates the SCL expression, which is the factor for patterning the mesoderm during gastrulation. But this stage for patterning the mesoderm is too broad for the man skilled in the art to anticipate the role of a Mix-like homeobox gene differentiating the hematopoietic stem cell into the NK cell.

D3 and D4 also designate the role of c-Myb to determine the fate of the endothelial progenitors to the earliest precursor of hematopoietic cell lineage, not the differentiation of the NK cell diverged from the stem cell, which is the main function of the composition of this invention.

In D5, the c-Myc activates the NK cell induced cytolysis at a post-triggering stage of NK cell-target cell interaction. The activation of NK cell induced cytolysis is related to the function of a mature NK cell. The subject matter of this invention differs from the teaching of D5 in that the c-Myc regulates the differentiation into a mature NK cell. The skilled person cannot anticipate the role of c-Myc for the differentiation into the mature NK cell, out of the NK cell induced cytolysis as disclosed in D5.

Therefore, the subject matter of this invention seems to involve an inventive step under PCT Article 33(3).

III. Industrial Applicability

The subject matter of claims 1-7 is considered to be industrially applicable under PCT Article 33(4).

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